Effect of Vitamin E and Beta Carotene on the Incidence of Angina Pectoris

A Randomized, Double-blind, Controlled Trial

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Objective.—To examine the effect of supplementation with vitamin E (alpha tocopherol), beta carotene, or both on the incidence of angina pectoris in men without known previous coronary heart disease.

Design.—Randomized, double-blind, placebo-controlled trial.

Setting and Participants.—Participants in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study (N=29 133) were male smokers aged 50 through 69 years who were living in southern and western Finland. Of these men, 22 269 were considered free of coronary heart disease at baseline and were followed up for the incidence of angina pectoris.

Intervention.—Participants were randomized to receive 50 mg/d of alpha tocopherol, 20 mg/d of beta carotene, both, or placebo in a 2×2 design.

Outcome Measures.—An incident case was defined as the first occurrence of typical angina pectoris identified in administering the annually repeated World Health Organization (Rose) Chest Pain Questionnaire.

Results.—During a median follow-up time of 4.7 years (96 427 person-years), 1983 new cases of angina pectoris were detected. Comparing alpha tocopherol–supplemented subjects with non–alpha tocopherol–supplemented subjects showed a relative risk (RR) of angina pectoris incidence of 0.91 (95% confidence interval [CI], 0.83 to 0.99; P=.04). The RR for incidence of angina pectoris for the beta carotene–supplemented subjects compared with those not receiving beta carotene was 1.06 (95% CI, 0.97 to 1.16; P=.19). Compared with those receiving placebo, the RRs for incidence of angina pectoris were 0.97 (95% CI, 0.85 to 1.10) and 0.96 (95% CI, 0.85 to 1.09) in the alpha tocopherol and alpha tocopherol plus beta carotene groups, respectively, and 1.13 (95% CI, 1.00 to 1.27) in the beta carotene group (P=.06). Baseline dietary intakes and serum levels of alpha tocopherol and beta carotene did not predict incidence of angina pectoris.

Conclusions.—Supplementation with alpha tocopherol was associated with only a minor decrease in the incidence of angina pectoris. Beta carotene had no preventive effect and was associated with a slight increase in the incidence of angina.

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EVIDENCE is accumulating from both laboratory and epidemiological studies that oxidative modification of low-density lipoprotein may have a key role in the development of atherosclerosis. Alpha tocopherol (vitamin E) supplementation has been shown to protect human low-density lipoprotein against oxidation.[1-5] Beta carotene in vitro has been reported to inhibit lipoprotein oxidation,[6] but its role in vivo remains controversial.[7,8] However, it has been suggested that beta carotene may inhibit the ability of cells to oxidize lipoproteins.[9] In addition to their antioxidant function, these vitamins have other biological effects. For instance, alpha tocopherol has been shown in vitro to decrease platelet adhesion,[10] inhibit smooth-muscle cell proliferation and protein kinase C activity,[11] and inhibit interleukin-1β expression.[12] Thus, both alpha tocopherol and beta carotene can be hypothesized to affect atherosclerosis and its clinical manifestations, especially coronary heart disease (CHD).

See also p 699.

Studies of antioxidant vitamin consumption,[13-16] plasma levels,[17-20] and adipose tissue concentration[21] suggest a protective effect against CHD. Thus far, studies have been mainly observational, follow-up, or case-control studies. Only two controlled studies of the effects of antioxidant vitamin supplementation on CHD have been published to date. In the Physicians' Health Study, supplementation with 50 mg of beta carotene on alternate days reduced major coronary events by 44% among physicians with a history of chronic stable angina or prior coronary revascularization.[22] In the Finnish Alpha Tocopherol, Beta Carotene Cancer Prevention (ATBC) Study, of which this study is a part, there were fewer

deaths due to CHD among the subjects receiving alpha tocopherol supplementation (50 mg/d) than among subjects not receiving alpha tocopherol, but more CHD deaths were observed among subjects receiving beta carotene supplements (20 mg/d) than among those not receiving beta carotene.[23]

Angina pectoris is the mildest and often first clinical manifestation of CHD. To our knowledge, no controlled trials of prevention of angina pectoris by antioxidant supplementation have previously been published. We report herein the results of a study of the incidence of angina pectoris in a controlled trial of alpha tocopherol and beta carotene supplementation.

METHODS

The study population comprises the participants in the ATBC Study. Study design, methods, participant characteristics, and compliance have been reported in detail previously.[24]

Subjects

To be eligible for the ATBC Study, the subjects had to be men aged 50 to 69 years who smoked five or more cigarettes daily, lived in the study area in southwestern Finland, and were willing to participate with written informed consent. Exclusion criteria were proven malignancy (except nonmelanoma skin cancer or cancer in situ), severe angina pectoris (typical angina on walking on level ground), chronic renal insufficiency, cirrhosis of the liver, chronic alcoholism, anticoagulant therapy, other medical problems that might limit participation, and current use of supplements containing vitamin E, vitamin A, or beta carotene.

The participants of the ATBC Study were recruited by a postal questionnaire from the total male population aged 50 to 69 years living in the area (n=290 406). Men who reported smoking five or more cigarettes daily and were willing to participate in the study (n=42 957) were invited to undergo baseline examinations. From these men, after eligibility assessments, the final study group (N=29 133) was formed.

The subjects were randomly assigned to one of the following supplementation groups in a 2×2 factorial design: 50 mg/d of alpha tocopherol (as *dl*-alpha tocopherol acetate), 20 mg/d of beta carotene, 50 mg/d of alpha tocopherol and 20 mg/d of beta carotene, or placebo. This allowed evaluation of the two agents in a single trial, provided that there was no interaction. Enrollment of the study participants took place from 1985 through 1988, and the intervention continued until April 30, 1993.

Men with known CHD at baseline were excluded. Subjects were considered to have CHD if they had a history of angina pectoris or myocardial infarction based on a diagnosis made by a physician or reported symptoms of typical angina pectoris or possible myocardial infarction during administration of the chest pain questionnaire. At baseline, 6864 subjects met at least one of these criteria and were excluded (1716 randomized to alpha tocopherol, 1680 to beta carotene, 1730 to both, and 1738 to placebo), leaving 22 269 subjects for follow-up. Of these, 5570 received alpha tocopherol, 5602 beta carotene, 5548 alpha tocopherol and beta carotene, and 5549 placebo. Thus, according to the 2×2 factorial design, approximately half (n=11 118) received alpha tocopherol and half (n=11 151) did not, and similarly, approximately half (n=11 150) received beta carotene and half (n=11 119) did not.

The study was approved by the institutional review boards of both the National Public Health Institute, Helsinki, Finland, and the National Cancer Institute, Bethesda, Md.

Baseline Assessments, Follow-up, and End Points

At baseline the men completed questionnaires on general background characteristics and medical, smoking, and occupational history. Frequency of leisure-time physical activity (at least slightly strenuous activity for a minimum of 30 minutes at a time) was categorized as follows: less than once a week, once or twice per week, and three or more times per week. The customary diet was assessed by a detailed diet-history questionnaire, which also measured ethanol intake.[25] For analytical purposes, ethanol intake was classified into three groups: nonusers, those who consumed 30 g or less of ethanol per day, and those who consumed more than 30 g of ethanol per day. Height and weight were measured, and body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured from the right arm with a mercury sphygmomanometer under standardized conditions. The lower of two measurements at least 1 minute apart was recorded. Serum samples were collected and stored at −70°C for later analysis.

The World Health Organization (Rose) Chest Pain Questionnaire[26] for angina pectoris and possible myocardial infarction was administered in an interview by trained study nurses at baseline and annually thereafter. Angina was considered typical if a subject reported (*a*) pain, discomfort, heaviness, or pressure in the chest on exertion, (*b*) relieved by rest (*c*) in 10 minutes or less, and (*d*) situated at the upper or lower sternal area or on the left side of the chest and in the left arm. Angina was considered atypical if it was brought on by exertion but did not fulfill all the additional criteria of typical angina. Myocardial infarction was considered possible if the subject reported having had severe chest pain lasting for 30 minutes or more.

The follow-up consisted of three visits per year to a local study center. Once a year a more comprehensive evaluation was made, including readministration of the chest pain questionnaire. After 3 years of supplementation, a serum sample was taken. Follow-up continued for a maximum of 7 years (median, 4.7 years), until typical angina pectoris was identified in administering the questionnaire, or until the last visit when the questionnaire was administered, for a total of 96 427 person-years. A dropout was considered to occur when a subject, for any reason, failed to attend all later visits when the questionnaire was to be administered.

The primary end point was typical angina pectoris. To test for the effect of end point definition, we created two additional end points: first, atypical chest pain was included as an end point (which added more cases but decreased specificity), and second, only subjects reporting typical angina pectoris during two of three consecutive questionnaire administrations were considered to have angina pectoris (which decreased the number of cases but possibly added specificity). Repeatability of reported typical angina pectoris in the questionnaire remained relatively stable throughout the follow-up. Of subjects who reported typical angina pectoris at one visit and attended the visit when the questionnaire was readministered a year later, about 38% reported typical angina pectoris again.

The study capsules were counted at every follow-up visit. Overall compliance was defined as a percentage calculated by dividing the number of capsules taken by the number of days in the trial.

Laboratory Measures

Serum levels of alpha tocopherol and beta carotene were determined from the baseline and 3-year samples using high-performance liquid chromatography assay.[27] Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically (CHOD-PAP method, Boehringer Mannheim, Mannheim, Germany).[28,29]

Statistical Analysis

An incident case of angina pectoris was defined as the first occurrence of typical chest pain identified at the annual administration of the chest pain question-

naire. The treatment-specific cumulative incidence of angina pectoris was calculated by the Kaplan-Meier method, using the Mantel-Haenszel test to calculate statistical significance for difference between the treatments. Cox proportional hazards regression was used to calculate the relative risk of angina pectoris. Regression models were made with supplementations as explanatory variables with and without adjustment for the baseline characteristics of the participants. Continuous variables were divided into tertiles in the regression models. To eliminate the effect of local differences in baseline hazard, the model was stratified according to the 14 local study centers. The associations of tertiles of baseline dietary intakes and serum levels of alpha tocopherol and beta carotene with the incidence of angina pectoris were calculated by Cox regression in the placebo group. The proportional hazards assumption was tested and not rejected. Interactions between the supplementation groups and between supplementations and background variables were tested by comparing nested Cox models with the likelihood ratio test. The background variables were age, body mass index, number of daily cigarettes, total serum cholesterol and HDL cholesterol levels, systolic and diastolic blood pressure, ethanol intake, frequency of leisure-time physical activity, and serum levels and dietary intakes of alpha tocopherol and beta carotene.

For subjects who had serum samples obtained both at baseline and at 3 years and had not yet experienced angina pectoris, the change in the serum level of alpha tocopherol or beta carotene caused by supplementation was calculated. The effect of the change on subsequent incidence of angina pectoris was analyzed separately for the alpha tocopherol– and beta carotene–supplemented subjects by proportional hazards regression, adjusting for the respective baseline serum level and baseline serum total cholesterol.

RESULTS

At study entry, the participants had a median age of 56.9 years, smoked a median of 20 cigarettes a day, and had a median total cholesterol level of 6.1 mmol/L (236.0 mg/dL). No between-group differences in baseline characteristics by supplementation group were observed (Table 1). According to the regression models, higher values for age, body mass index, number of daily cigarettes, total cholesterol, and systolic blood pressure were associated with increased incidence of angina pectoris, whereas increased HDL cholesterol level and high diastolic blood pressure were associated with decreased angina incidence. Daily ethanol intake and frequency of physical activity had no significant effect. Overall dropout rates were 26.2% in the alpha tocopherol group, 27.3% in the beta carotene group, 27.1% in the alpha tocopherol plus beta carotene group, and 26.6% in the placebo group. Overall capsule compliance during active study participation was 94% in all four supplementation groups.

Table 1.—Baseline Characteristics by Supplementation Group in the ATBC Study*

Characteristic	Alpha Tocopherol	Beta Carotene	Alpha Tocopherol + Beta Carotene	Placebo
No. of subjects	5570	5602	5548	5549
Age, y	56.9	56.9	57.1	56.7
Cigarettes/d	20	20	20	20
Serum cholesterol, mmol/L (mg/dL)	6.1 (236.0)	6.1 (236.0)	6.1 (236.0)	6.1 (236.0)
HDL cholesterol, mmol/L (mg/dL)	1.1 (42.5)	1.1 (42.5)	1.1 (42.5)	1.1 (42.5)
Body mass index, kg/m²	26.0	26.0	26.0	26.0
Systolic blood pressure, mm Hg	140	140	140	140
Diastolic blood pressure, mm Hg	88	88	88	88
Daily ethanol use, g	11	11	11	11
Physical activity at least once a week, %	49	49	48	47

*Data for characteristics are median values. ATBC indicates Alpha Tocopherol, Beta Carotene Cancer Prevention; and HDL, high-density lipoprotein.

Table 2.—Incidence and Relative Risk of Angina Pectoris by Supplementation With Either Alpha Tocopherol or Beta Carotene

Supplementation	No. of Cases	Incidence per 1000 Person-Years	Relative Risk (95% Confidence Interval)
Alpha tocopherol	948	19.6	0.91 (0.83-0.99)
No alpha tocopherol	1035	21.5	1.00
Beta carotene	1020	21.2	1.06 (0.97-1.16)
No beta carotene	963	20.0	1.00

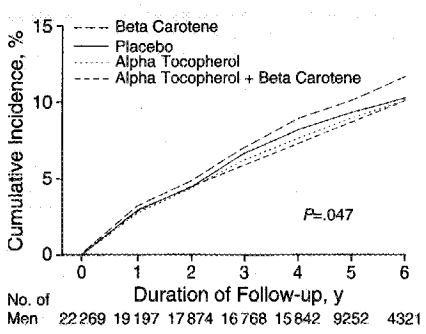
A total of 1983 new cases of angina pectoris were observed during follow-up. There was no interaction between the two supplements in their effect on incidence (likelihood ratio test, P=.12). The incidence of angina pectoris was 9% lower in the subjects who received alpha tocopherol than in those who did not (95% confidence interval [CI] for difference, –17% to –1%; P=.04). Subjects receiving beta carotene had a 6% higher incidence than those not receiving it (95% CI for difference, –3% to 16%; P=.19) (Table 2). Adjusting for age, body mass index, number of daily cigarettes, total and HDL cholesterol, systolic and diastolic blood pressure, ethanol intake, and frequency of leisure-time physical activity did not markedly alter the results. There were no interactions between the supplementations and the background variables. In the group with serum level measurements of alpha tocopherol and beta carotene both at baseline and at 3 years, changes in the levels among subjects with the respective supplementations were not associated with the risk of later angina pectoris.

The same calculations were made using the alternative definitions of the end point, ie, typical and atypical angina together, and typical angina present in two of three consecutive chest pain interviews. Both end points produced similar results: alpha tocopherol slightly (nonsignificantly) decreased the incidence of angina pectoris, and beta carotene had no effect.

Kaplan-Meier curves of cumulative incidence by the four original supplementation groups are shown in the Figure, and incidence rates and relative risks are shown in Table 3. Compared with placebo, the incidence of angina was approximately 3% lower in the alpha tocopherol group (95% CI for difference, –15% to 10%; P=.63) and 4% lower in the alpha tocopherol plus beta carotene group (95% CI for difference, –15% to 9%; P=.58). The beta carotene group had a 13% higher incidence of angina (95% CI for difference, 0% to 27%; P=.06) than the placebo group. Adjusting for the baseline characteristics brought no relevant changes to the results.

The alternate end points were also tested in the four supplementation groups. Slight changes in relative risks (compared with the primary end point) were observed, but neither alternative brought forth any significant findings.

Associations of baseline dietary intakes and serum levels of alpha tocopherol and beta carotene with the incidence of angina pectoris in the placebo group are shown in Table 4. Dietary intake of alpha tocopherol had no association with the incidence of angina pectoris. The incidence was lower in the



Kaplan-Meier curves of cumulative incidence of angina pectoris in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study by supplementation group. The *P* value refers to the differences among all four supplementation groups, obtained from the Mantel-Haenszel test.

Table 3.—Incidence and Relative Risk of Angina Pectoris by Supplementation With Alpha Tocopherol, Beta Carotene, Both, or Placebo

Supplementation	No. of Cases	Incidence per 1000 Person-Years	Relative Risk (95% Confidence Interval)
Alpha tocopherol	476	19.7	0.97 (0.85-1.10)
Beta carotene	548	22.8	1.13 (1.00-1.27)
Alpha tocopherol + beta carotene	472	19.6	0.96 (0.85-1.09)
Placebo	487	20.2	1.00

Table 4.—Baseline Dietary Intakes and Serum Levels of Alpha Tocopherol and Beta Carotene in Tertiles, and Corresponding Adjusted Relative Risks for the Incidence of Angina Pectoris in the ATBC Study, Placebo Group Only*

	Tertile		
Baseline Value	Lowest	Middle	Highest
Dietary intake			
Alpha tocopherol, mg/d	<8.5	8.5-12.4	>12.4
RR (95% CI)	1.00	0.97 (0.77-1.22)	1.12 (0.89-1.41)
Beta carotene, mg/d	<1.2	1.2-2.3	>2.3
RR (95% CI)	1.00	0.69 (0.55-0.87)	0.91 (0.73-1.14)
Serum level			
Alpha tocopherol, μmol/L (mg/dL)	<23.9 (<1.03)	23.9-29.3 (1.03-1.26)	>29.3 (>1.26)
RR (95% CI)	1.00	0.89 (0.70-1.14)	0.90 (0.68-1.19)
Beta carotene, μmol/L (μg/dL)	<0.24 (<13.1)	0.24-0.42 (13.1-22.5)	>0.42 (>22.5)
RR (95% CI)	1.00	0.81 (0.65-1.03)	0.84 (0.66-1.07)

*Adjusted for tertiles of age, body mass index, number of daily cigarettes, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, classes of ethanol intake (nonusers, 1-30 g/d, and >30 g/d), and frequency of leisure-time physical activity (<once per week, 1 to 2 times per week, and ≥3 times per week). ATBC indicates Alpha Tocopherol, Beta Carotene Cancer Prevention; RR, relative risk; and CI, confidence interval.

middle tertile of beta carotene intake than in the highest and lowest tertiles. The relative risks of the dietary intakes were not affected by adjustment for baseline characteristics. The highest tertile of baseline serum alpha tocopherol was positively but nonsignificantly associated with the incidence of angina pectoris, but after we adjusted for baseline characteristics the association became negative but still nonsignificant. The explanation for this change most probably was the close relationship between alpha tocopherol and cholesterol in serum. A nonsignificant decrease in both unadjusted and adjusted relative risks was associated with higher serum levels of beta carotene.

COMMENT

This double-blind, placebo-controlled primary prevention study showed that subjects receiving 50 mg/d of alpha tocopherol had a lower incidence of angina pectoris than those not receiving it. Subjects receiving 20 mg/d of beta carotene had a nonsignificant increase in incidence in comparison to those not receiving it. Comparing the three supplemented groups with the placebo group showed a nonsignificant decrease in the incidence of angina pectoris in the alpha tocopherol and alpha tocopherol plus beta carotene groups. Subjects in the beta carotene group had a higher incidence of angina pectoris, a finding of borderline statistical significance. Changes in the serum levels of alpha tocopherol and beta carotene among subjects with the respective supplementations were not associated with the incidence of angina pectoris.

Certain factors should be considered in evaluating these results. Because of the size of the study groups, which were balanced according to known risk factors of CHD, bias is unlikely. The magnitude of the study groups also makes it reasonable to assume balance in other factors possibly related to angina pectoris, such as medication use. Dropout rates were similar in all the supplementation groups. If dropout were somehow associated with the end point, it would result in dilution of the supplementation effect. Compliance throughout active study participation was virtually identical in all supplementation groups. Subjects were middle-aged and elderly male smokers, and therefore do not represent the general population. Instead, these subjects probably have a higher level of oxidative stress and thus represent a group potentially benefiting more from supplemental antioxidants. Nevertheless, the classic risk factors of CHD were associated with the incidence of angina pectoris in the regression models.

Angina pectoris symptoms were assessed annually by the World Health Organization (Rose) Chest Pain Questionnaire. This questionnaire has been widely used in epidemiological studies since its introduction in 1962,[26] and its findings correlate well with clinical diagnoses and electrocardiographic changes; a sensitivity of 81% to 83% and specificity of 97% to 100% have been reported.[30,31] A Finnish study reported a sensitivity and specificity of 56% and 77%, respectively, compared with a clinician's diagnosis.[32] Compared with angiographic findings these figures were 18% and 81%,[33] respectively, and compared with exercise thallium scintigraphy findings they were 44% and 77%,[34] respectively. Despite these modest correlations with more exact diagnostic methods, the predictive value of the questionnaire for angina pectoris is good. Rose found that subjects reporting typical angina in the questionnaire had a 4-year relative risk of 5.0 for CHD and a 2-year relative risk of 4.8 for total mortality.[35] In the Whitehall study, typical angina pectoris in the questionnaire carried a relative risk of 5.0 for 5-year CHD mortality,[36] and in a Finnish study it carried a relative risk of 7.2 for 5-year cardiovascular mortality.[37]

Variability in questionnaire responses is known to be substantial, and probably reflects a combination of true physiological variability in chest pain and variability in answering the questionnaire. Repeatability is correlated with the severity of symptoms[38] and decreases with time.[32] Repeatability at 1 year has been 35% to 40% in different studies[32,38,39]; in the British Regional Heart Study it was 39% at 5 years.[40] In our study repeatability was comparable, approximately 38% during follow-up.

It is realistic to assume some degree of misclassification in the end point of angina pectoris. However, there is no reason to believe that it is associated with supplementation group. Misclassification of the end point leads to some degree of underestimation of the supple-

mentation effect.[41] Because of the known problems of end point assessment by the questionnaire, we evaluated the effect of different end point definitions. As these analyses yielded similar results, we concluded that our primary end point of first occurrence of typical angina pectoris was appropriate.

The dose of beta carotene was 20 mg per day, comparable to that used in the Physicians' Health Study, in which a beneficial effect in secondary prevention of CHD has been reported.[22] The vitamin E supplementation was 50 mg of *dl*-alpha tocopherol acetate per day. While this dose is relatively low by current opinion, at the beginning of the study in the early 1980s, little was known of the effects of different doses or prolonged supplementation. Two recent studies have shown that increasing the supplemental dose of vitamin E up to 800 to 1200 IU per day (1 IU = 1 mg of *dl*-alpha tocopherol acetate) results in increased resistance of low-density lipoprotein to in vitro oxidation.[4,42] The clinical significance of these in vitro results is still unknown.

According to the National Research Council of the United States, the recommended dietary allowance for vitamin E is 10 mg of *d*-alpha tocopherol equivalents,[43] so the supplementation in this study was 3.7-fold by comparison. In the Nurses' Health Study,[14] the relative risk of CHD decreased in the quintile with an intake range of 8.1 to 21.5 IU per day. In the Health Professionals Follow-up Study,[13] the relative risk for CHD diminished with supplemental intake of vitamin E of less than 25 IU per day, although a significant effect was first seen with an intake of 100 IU or more per day.

The median duration of follow-up in our study was 4.7 years, which is a relatively short time in the natural history of evolving atherosclerosis. In the Nurses' Health Study[14] and the Health Professionals Follow-up Study,[13] the protective effect was linked to prolonged use of vitamin E, but was seen already after 2 years of vitamin use.

Several alternative explanations should be considered in interpreting our results. In light of the incidence data in the four original supplementation groups, it seems possible that in the 2×2 factorial comparison of alpha tocopherol supplementation to no alpha tocopherol supplementation there is no true protective effect; instead, the apparent effect might be caused by a higher incidence of angina in the no alpha tocopherol group (since half of these subjects received beta carotene). Statistical analyses did not reveal interaction between alpha tocopherol and beta carotene supplementation, and we know of no firm biological basis for it. As one possible explanation, it can be theorized that for some reason beta carotene in this setting was harmful (eg, pro-oxidant), an effect inhibited in the combination with alpha tocopherol, which, in turn, by itself only minimally decreased the incidence of angina pectoris. Finally, the possibility of a high or low incidence of angina in some group caused by chance cannot be excluded.

Angina pectoris is only one manifestation of CHD. Thus, these results do not allow direct conclusions on the effects of the supplementations on other, more severe events caused by CHD. We know of no other similar trial studying the effect of alpha tocopherol or beta carotene on the incidence of angina pectoris. Thus far, the only published report of CHD prevention is that of Gaziano et al,[22] who evaluated the effect of beta carotene supplementation on the incidence of coronary revascularization, fatal CHD, and nonfatal myocardial infarction and observed a risk reduction of 44%. The 333 subjects had previous CHD and the end points were different from ours, so direct comparisons are not possible. Moreover, the number of cases was small. Further evidence for a possible effect of vitamin E supplementation comes from the Nurses' Health Study[14] and the Health Professionals Follow-up Study,[13] which studied the association of antioxidant vitamin intake and the incidence of CHD. In both of these observational studies, use of vitamin E supplements was associated with decreased risk of subsequent coronary events.

In the ATBC Study, of which this study is a part, ischemic heart disease mortality was lower in the alpha tocopherol group than in the no alpha tocopherol group and higher in the beta carotene group than in the no beta carotene group.[23] Although the present data suggest a similar effect, comparisons between angina pectoris incidence and CHD mortality must be made with caution.

In the placebo group, a significant decrease in the incidence of angina pectoris was observed in the middle tertile of dietary beta carotene intake, but in the highest intake tertile the association diminished and was nonsignificant. The tertiles for the middle third of beta carotene intake were 1.2 mg to 2.3 mg. It seems improbable that a true biological effect in such a narrow range of dietary intake exists. Thus, we conclude that chance is the most probable explanation for this observation.

Serum levels of alpha tocopherol and beta carotene were not significantly associated with the risk of angina pectoris incidence in our study. In a case-control study in Scotland, Riemersma et al[17] found a statistically significant adjusted odds ratio of 2.68 for angina pectoris between the lowest and highest quintiles of serum vitamin E concentrations. Adjusted odds ratios for serum levels of vitamins A and C and beta carotene were not significant in their study.

Cross-cultural studies have shown inverse correlations between serum antioxidant vitamin concentrations and ischemic heart disease mortality.[18,44] An association between low serum levels of carotenoids and a high risk of CHD has recently been reported in two studies.[19,20] Bellizzi et al[16] found a strong negative association between alpha tocopherol in diet and CHD mortality rates. The design and end points of these studies make comparisons with our study difficult. Lack of association of serum levels of vitamin E and risk of myocardial infarction has also been demonstrated.[45]

Vitamin E in the treatment of angina pectoris has been studied in two well-designed placebo-controlled clinical trials.[46,47] The treatment time in these was 9 weeks to 6 months, so these studies tested acute antianginal effects rather than an antiatherogenic effect. No convincing relief in symptoms or improvement in exercise capacity was observed in either study.

In conclusion, we found evidence of a preventive effect of alpha tocopherol supplementation on angina pectoris, but the effect was small and hardly of public health significance. Beta carotene supplementation had no preventive effect; in fact, a slight increase in the incidence of angina pectoris was observed.

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